Sox2 haploinsufficiency primes regeneration and Wnt responsiveness in the mouse cochlea.

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Public Summary:
The neonatal mouse cochlea is able to regenerate lost sensory hair cells required for hearing. Here we found that levels of a transcription factor Sox2 modulates the level of hair cell regeneration at this developmental age. Moreover, Wnt signaling is a fundamentally important pathway that fuels regeneration in many tissues. We found that modulation of Sox2 enhances responsiveness to Wnt signaling. These results suggest a combinatorial approach is feasible and promising in modulating mammalian inner ear hair cell regeneration.

Scientific Abstract:
During development, Sox2 is indispensable for cell division and differentiation, yet its roles in regenerating tissues are less clear. Here, we used combinations of transgenic mouse models to reveal that Sox2 haploinsufficiency (Sox2haplo) increases rather than impairs cochlear regeneration in vivo. Sox2haplo cochleae had delayed terminal mitosis and ectopic sensory cells, yet normal auditory function. Sox2haplo amplified and expanded domains of damage-induced Atoh1+ transitional cell formation in neonatal cochlea. Wnt activation via beta-catenin stabilization (beta-cateninGOF) alone failed to induce proliferation or transitional cell formation. By contrast, beta-cateninGOF caused proliferation when either Sox2haplo or damage was present, and transitional cell formation when both were present in neonatal, but not mature, cochlea. Mechanistically, Sox2haplo or damaged neonatal cochleae showed lower levels of Sox2 and Hes5, but not of Wnt target genes. Together, our study unveils an interplay between Sox2 and damage in directing tissue regeneration and Wnt responsiveness and thus provides a foundation for potential combinatorial therapies aimed at stimulating mammalian cochlear regeneration to reverse hearing loss in humans.